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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,821	02/25/2002	Jay D. Hunt III	00M28. 1 Hunt	1308

25547 7590 05/26/2004

PATENT DEPARTMENT
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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,821	HUNT ET AL.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *the remarks of 22 DEC 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-10 are pending.

2. Claims 1-10 are rejected.

Response to Arguments

3. Applicants' arguments filed December 22, 2003 have been fully considered but they are not persuasive with respect to the rejections under 35 U.S.C. 112, first paragraph. Applicants present the following arguments. First, applicants allege that there is adequate written description in the instant specification for the functionally written phrase, "a bFGF-active PAF antagonist." Second, applicants purport that because instant claim 1 is not directed to inhibiting the growth of any tumor but rather to inhibiting the growth of a tumor that depends on basic fibroblast growth factor-stimulated angiogenesis. Third, applicants argue that the prior art reference of Hunt et al. is not prior art, since it was not published. Although this is true the, prior art reference of Hunt et al., abstract 4099, of Proceedings of the American Association of Cancer Research: Cell and Tumor Biology, vol. 41, (2000), is germane and relevant prior art. Accordingly the rejections under 102 and 103 are now made in view of Hunt et al. Hunt et al., abstract 4099, of Proceedings of the American Association of Cancer Research: Cell and Tumor Biology, vol. 41, (2000).

4. First, applicants allege that there is adequate written description in the instant specification for the functionally written phrase, "a bFGF-active PAF antagonist."

Although there is support for phrase a bFGF-active PAF antagonist for the compounds of BN-50730 and CV 3988, the instant specification has insufficient descriptive support for the broad functional phrase of a "bFGF-active PAF antagonist" in the instant specification. In addition, the instant specification does not describe what is meant by the functional characteristics of being known as a bFGF-active PAF antagonist. Moreover, the phrase, "a bFGF-active PAF antagonist" not only functionally describes compounds at the time of the filing of this invention but also embraces compounds not yet known or discovered. Applicants also have not provided one skilled in the art with any structural identifying characteristics of the phrase a "bFGF-active PAF antagonist." Because there is no evidence, such as with review articles or assays, that there is any per se structure/function relationship between the disclosed phrase of a "bFGF-active PAF antagonist" and any others that might be found using the claimed method, the instant specification fails to adequately describe this broad functional recitation of compounds other than the compounds of BN-50730 and CV 3988.

5. Second, applicants purport that because instant claim 1 is not directed to inhibiting the growth of any tumor but rather to inhibiting the growth of a tumor that depends on basic fibroblast growth factor-stimulated angiogenesis. The only inhibiting tumors of carcinoma that are enabled in the present specification are those of lung and prostate cancer *and only* with the administration of bFGF-active PAF antagonist compound of BN-50730. In addition, this is supported by the administration of BN-50703 to mice that were implanted with human prostatic carcinoma cells, PC-3, and the lung adenocarcinoma cell line 201T, (see Examples 7 and 3, respectively). Accordingly,

there is no correlation between the administration of all, let alone future, bFGF-active PAF antagonist compounds for the treatment of numerous types of cancers. This is supported by the fact that the instant specification only

Claim Rejections - 35 USC § 112

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. The rejection of claims 1, 4 and 6-10 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained and repeated for both the above-stated and reasons of record. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Independent claim 1 is directed to a method of inhibiting the growth of a tumor in a mammal, wherein the growth of the tumor depends on basic fibroblast growth factor-stimulated angiogenesis with the administration of a bFGF-active PAF antagonist. This claim fails to meet the written description requirement for the following reasons. The term a bFGF-active PAF antagonist is written functionally. There is insufficient descriptive support for the functional term a bFGF-active PAF antagonist in the instant specification. In addition, the instant specification does not describe what is meant by the functional characteristics of being known as a bFGF-active PAF antagonist. Structural identifying characteristics of the term a bFGF-active PAF antagonist are not disclosed to one

skilled in the art. There is no evidence that there is any per se structure/function relationship between the disclosed term of a bFGF-active PAF antagonist and any others that might be found using the claimed method. Furthermore, there is no support that the particularly disclosed term of a bFGF-active PAF antagonist is represented by the sole examples of BN-50730 and CV 3988. Thus, these claims fail to comply with the written description requirement. In the absence of some understanding of the functional term a bFGF-active PAF antagonist other than the adequately described BN-50730 and CV 3988, the artisan would not have accepted that the applicant was in possession of the claimed method as currently written.

8. The rejection of claims 1-8 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting tumors of carcinoma of the lung and prostate, does not reasonably provide enablement for carcinomas of the breast, colon, stomach, pancreas, skin, uterus, cervix, mouth, larnyx, esophagus, liver, kidney; sarcomas of the muscle or connective tissue; osteosarcomas; neuroblastomas; glioblastomas; neuroblastomas; Hodgkin's disease lymphomas; non-Hodgkin's lymphomas; B-cell lymphomas; T-cell lymphomas; acute lymphocytic leukemias; chronic myloid leukemia; acute myloid leukemia; and non-malignant tumors is maintained and repeated for both the above-stated and reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to for inhibiting tumors. The method comprises administering the bFGF-active PAF antagonist compounds of BN-50730 or CV 3988

(2) The state of the prior art

The compounds of the prior art of Montrucchio et al. are directed to inhibiting neovascularization with the PAF receptor antagonist of WEB 2170.

(3) The relative skill of those in the art

The relative skill of those in the art of cancer pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art); In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of treating all tumors prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to inhibiting the growth of any tumor with bFGF-active PAF antagonist. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of

the physiological or pharmaceutical activity of a bFGF-active PAF antagonist to be effective in treating or inhibiting the growth of tumors is insufficient for enablement. The specification provides no guidance, in the way of enablement for inhibiting tumors of carcinoma of the lung and prostate, does not reasonably provide enablement for carcinomas of the breast, colon, stomach, pancreas, skin, uterus, cervix, mouth, larnyx, esophagus, liver, kidney; sarcomas of the muscle or connective tissue; osteosarcomas; neuroblastomas; glioblastomas; neuroblastomas; Hodgkin's disease lymphomas; non-Hodgkin's lymphomas; B-cell lymphomas; T-cell lymphomas; acute lymphocytic leukemias; chronic myloid leukemia; acute myloid leukemia; and non-malignant tumors other than inhibiting tumors of carcinoma of the lung and prostate. The specification provides no guidance, in the way enablement for the treatment or inhibition of tumors of carcinoma of the lung and prostate, does not reasonably provide enablement for carcinomas of the breast, colon, stomach, pancreas, skin, uterus, cervix, mouth, larnyx, esophagus, liver, kidney; sarcomas of the muscle or connective tissue; osteosarcomas; neuroblastomas; glioblastomas; neuroblastomas; Hodgkin's disease lymphomas; non-Hodgkin's lymphomas; B-cell lymphomas; T-cell lymphomas; acute lymphocytic leukemias; chronic myloid leukemia; acute myloid leukemia; and non-malignant tumors. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Accordingly, this is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d

235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses inhibiting tumors of carcinoma of the lung and prostate with the bFGF-active PAF antagonist compounds. However, the instant specification only has enablement for inhibiting tumors of carcinoma of the lung and prostate.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative,

since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the types of tumors that are inhibited with the bFGF-active PAF antagonist compounds that would be enabled in this specification.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1 and 4-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following explanation supports this rejection. These claims are directed to the administration of a functionally written compounds that are described as bFGF-active PAF antagonist compounds. Defining a compound by its function, namely as antagonizing the bFGF-active PAF renders these claims vague and indefinite because this functional recitation embraces compounds that are not yet synthesized. The test for determining compliance with 35 U.S.C. 112, second paragraph, is whether applicants have clearly defined "their" invention rather than what compounds may be discovered by future research as these claims are currently written.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Hunt et al., abstract 4099, of Proceedings of the American Association of Cancer Research: Cell and Tumor Biology, vol. 41, (2000). Hunt et al. teach of that PAF antagonist of BN 50730 inhibits basic fibroblast growth factor-induced proliferation. Hunt et al. also disclose of a significant reduction in tumor growth in BN 50730-treated mice versus untreated-mice, (see abstract). Hunt et al. further teach that BN 50730 can be combined with other antiangiogenic compounds in order to increase their efficacy, (see abstract).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunt et al., abstract 4099, of Proceedings of the American Association of Cancer Research: Cell and Tumor Biology, vol. 41, (2000). Hunt et al. teach of that PAF antagonist of BN 50730 inhibits basic fibroblast growth factor-induced proliferation. Hunt et al. also disclose of a significant reduction in tumor growth in BN 50730-treated mice versus untreated-mice, (see abstract). Hunt et al. further teach that BN 50730 can be combined with other antiangiogenic compounds in order to increase their efficacy, (see abstract). Because Hunt et al. teach that PAF is involved in the induction of angiogenesis, the skilled artisan would have been motivated to combine therapeutics in order to treat the very same ailment. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose,

in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

16. Although the prior art reference of Hunt et al. do not specifically recite the compounds of claim 5, Hunt et al. clearly state that BN 50730 can be combined with other antiangiogenic compounds in order to increase their efficacy. In addition, it is well within the general knowledge of those having ordinary skill in the art to determine optimum modes and methods of administration in order to obtain an effective therapeutic level of the active ingredient. This teaching provides motivation to the skilled artisan to utilize other antiangiogenic compounds to treat the very same ailment, in this case tumors. Clearly, it would have been obvious to the skilled artisan to include any compounds which inhibit angiogenesis along with BN 50730, as taught by Hunt et al., especially when they are both used for the very same purpose of treating or inhibiting tumors.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584. The official fax No. for correspondence is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
May 24, 2004